UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE NATIONAL PRESCRIPTION OPIATE LITIGATION **This document relates to**: *Track Three Cases*	**MDL No. 2804** **Case No. 17-md-2804** **Judge Dan Aaron Polster**

DECLARATION OF STEVEN N. HERMAN IN SUPPORT OF THE PHARMACY DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS AND TESTIMONY OF DR. KATHERINE KEYES

EXHIBIT 3

EXPERT REPORT OF KATHERINE KEYES, PHD

August 3, 2020

designed comparison groups to be the next level of evidence. Prospective follow-up is an important study design because it reduces biases in epidemiological studies from retrospective reporting of symptoms or events. Further, statistical controls are necessary to overcome the potential for bias from confounding. Prospective studies often involve comparison groups (e.g., prescription opioid users and a comparison group of non-prescription opioid users). Study designs with comparison groups provide evidence regarding opioid-related harm that is over and above harm in patient and general population samples across varying levels of opioid exposure. Studies of patient populations without comparison groups, however, are also informative particularly for research questions germane to the prevalence of opioid use disorders and related harm among patients prescribed opioids (especially high doses in long duration), as well as questions related to the proportion of drug users who previously used prescription opioids. Well-designed studies of single populations without explicit comparison groups are thus also considered by me as relevant evidence for characterization of prescription opioid-related harms.

With regard to studies that assess trends over time, I considered three data sources to be the highest levels of evidence. First, I relied on death records that are collected and harmonized by the national vital statistics surveillance system. While death records can have misclassification of causes of death, they are considered by experts to be a reliable indicator of national and local burden of specific causes of death, especially when examining trends over time. Second, I relied on data sources with a national reputation for transparency in reliability and validity that assess hospitalization and other clinical records, such as large electronic health databases, as well as national studies such as the National Inpatient Sample. Again, while such records can include misclassification, data sources gathered from reputable organizations such as the Agency for Healthcare Research and Quality include reliability and validity assessments that allow the researcher using them to be able to draw conclusions based on the best available evidence. Third, I relied on survey data that is routinely collected in the general population of households in the United States over time. Surveys are essential parts of surveillance, given that many cases of substance use disorder do not come to clinical attention, and thus relying on clinically ascertained records can give a biased assessment of trends and burden in the population. Survey data source methodology involves clustered sampling so that samples are representative of the entire United States, and respondents are interviewed with validated instruments that are designed to elicit diagnoses and information with maximum accuracy in the survey context. Generally, I do not include surveys that are not representative of the population, as they are not strong evidence for an assessment of the total burden and trends over time.

IV. DETAILED DISCUSSION OF OPINIONS AND REASONS AND BASES FOR THEM

A. Distribution, sales, and marketing of opioids increased in the 1990s

There is voluminous evidence regarding the increased distribution, sales, and marketing of opioids beginning in the 1990s. This evidence is the subject of other expert reports, and I will not repeat all of that evidence here. Instead, I will summarize some points for context. Opioid pain relievers became an increasingly widely-used option starting in the mid 1990s, particularly for chronic non-cancer pain, a use that had rarely been seen previously. Estimates from the Automation of Reports and Consolidated Orders System (ARCOS), which tracks prescription distribution and sales, indicate that prescription opioids were dispensed at an estimated 96 mg per person in 1997, and increased to 700 mg per person by 2007 (greater than 600% increase).[20,21] In 1995, the year OxyContin entered the market, the number of opioid prescriptions filled in the United States increased by 7 million, and continued to increase over the next two decades before peaking in the fourth quarter of 2012 at 62 million prescriptions dispensed.[22,23] From 1997 to 2002, prescriptions for OxyContin for non-cancer pain increased from approximately 670,000 in 1997 to about 6.2 million in 2002.[24] The increase in opioid prescribing was driven by a multitude of factors, including direct marketing to physicians using data that underestimated opioid use disorder risks in patients, which I will detail in Section B. Evidence shows that pharmaceutical marketing of prescription drugs increases prescribers' likelihood of prescribing the marketed drug in the future.[25,26] That is also true for prescription opioids; as a result, increasing marketing of opioid drugs led to increased sales of the marketed drugs.[27–29]

from the National Hospital Ambulatory Medical Care Survey and the National Ambulatory Medical Care Survey; opioid prescriptions were based on medication codes indicating whether hydrocodone, oxycodone, or a morphine-containing product were prescribed at each patient encounter (including 576,178 patient encounters). Prescription rates increased from 2-fold for hydrocodone, 2.64 for morphine, and 3.21 for oxycodone products from 1995 to 2004. Concomitantly, opioid-related emergency department visits based on Drug Abuse Warning Network (DAWN) data and respondent reports of non-medical opioid use based on NSDUH data increased across the same time period. Correlations between rates of prescription and rates of opioid-related ED visits and non-medical use were significant for hydrocodone (correlations ranged between 0.73 to 0.79) and oxycodone (correlations ranged from 0.76 to 0.87). Taken together, these data indicate strong and statistically significant correlations between opioid supply and opioid-related harm in the US population.

The relationship between opioid supply and opioid-related harm has been examined more recently as well. Ghertner (2019)[130] examined the relationship between opioid sales based on data from ARCOS with county-level opioid-related hospitalization rates based on counties in the states that report data to the Healthcare Cost and Utilization Program (HCUP) program. In a modeling strategy that used variation in Medicare Part D prescriptions as an instrumental variable to increase study rigor, as well as models that controlled for economic factors, there was a 9% increase in opioid-related hospitalizations for each one morphine kilogram equivalent increase in opioid sales. Further, results indicated that each morphine kilogram equivalent in sales resulted in a 14% increase in maternal and neonatal mortality. The relationship was specific to opioid-related hospitalizations, and was not associated with alcohol-related hospitalizations, underscoring the specificity of the association and increasing confidence in the validity of the results. Of note, data from West Virginia were included in the analysis conducted by Ghertner (2019), which analyzed on opioid distributions from ARCOS as well as opioid-related hospitalizations from the Healthcare Cost and Utilization Project. Thus, the findings reported by Ghertner (2019) includes the time frame and geographic distribution of West Virginia and its counties, which supports the opinion that the available data are consistent with a causal role of opioid supply on opioid-related harm specific to West Virginia and the Cabell Huntington Community. In totality, the multiple sources of evidence, cited above, consistently support the high correlation between opioid supply and opioid-related harm.

Further, the consistency of the association across other studies that measure opioid dispensing and sales with opioid related harm and mortality support my opinion that supply of opioids is causally associated with harm.[131] In 2009, Fisher et al. (2013) documented statistically significant and high correlations between the rate of hydromorphone dispensing and deaths due to hydromorphone, as well as the rate of oxycodone dispensing and deaths due to oxycodone. These correlations were high within-province, which is important because the base rates of overdose and dispensing varied by province and yet the correlations remained strong in each. Similar associations with non-fatal outcomes, such as substance abuse treatment admissions, have been published by the same investigators, indicating that the association between prescription opioid supply and opioid-related harms in Canada extends across outcomes related to opioid use disorder, as well as opioid overdose.[132]

The studies cited in the material above are based on associations, and alone are not sufficient in isolation to conclude a casual role of opioid distributions and opioid-related harm. This fact is acknowledged in the discussion section of these publications, however, building a scientific evidence base is not about the conclusion of one paper. I base my conclusion on the totality of evidence from across studies examining a variety of opioid prescribing and distribution measures, opioid-related morbidity and mortality outcomes, across a wide variety of geographic areas. The reliability of the observed association supports the opinion that there is a causal relationship.

The supply of opioids was also facilitated by pharmaceutical promotional activity to physicians. While I did not evaluate the specific marketing materials of the manufacturers, I did evaluate peer-reviewed epidemiological studies that document the association between opioid marketing with sales, which is germane to my expertise. Epidemiological evidence using statistical methods is routinely used to assess the association between exposure to pharmaceutical marketing and sales efforts with changes in prescribing, and has reliably

found across many studies in many populations that exposure to pharmaceutical marketing and sales is significantly associated with increases in prescribing of the marketed drugs. Indeed, available epidemiological evidence using rigorous quasi-experimental designs, such as difference-in-difference models, as well as controlling for numerous potential confounders, has consistently documented an association between the industry payments, meals, sales outreach to physicians, as well as pharmaceutical promotions, with increases in requests to add specific products to hospital formularies[133] as well as increases in rates of prescribing the marketed product.[134–137] These broader literatures provide a consistent evidence base when examining the associations between opioid marketing and opioid sales. Empirical evidence has demonstrated that industry payments to physicians as part of the marketing of prescription opioids were associated with increased opioid prescriptions,[138] and that 1 in 12 physicians in the US, and 1 in 5 family physicians, received opioid-related marketing.[26,138–140] Hadland et al. (2019)[141] used data form the Centers for Medicare & Medicaid Service Open Payments database to assess the monetary value in payments to physicians for opioid products in all US counties over time, as well as data on dispensing of opioids in available counties in the US, and examined the spatial and temporal correlations with prescription opioid deaths as designed in the vital statistics records. The authors used a rigorous statistical model that included controls for a range of county-level factors such as economic environment (e.g., unemployment, income, income inequality), as well as demographics. Results demonstrated that even with statistical controls in place, each one standard deviation increase in payments to physicians was associated with statistically significant increases in prescription opioid overdose, including when marketing was assessed by marketing value in dollars per capita (each standard deviation increase associated with 1.09 times the rate of death), number of payments to physicians per capita (each standard deviation increase associated with 1.18 times the rate of death), and number of physicians receiving marketing per capita (each standard deviation increase associated with 1.12 times the rate of death). Further, these authors conducted mediation analysis to quantitatively demonstrate that the association between marketing to physicians and prescription opioid overdose was mediated by (that is, explained by) the increase in opioid prescribing and increased distribution. However, it is important to note that payments to physicians are only one type of promotional activity, and accounted for only a proportion of the overall promotion strategy for opioid pharmaceuticals. These specific studies do not preclude potential effects of other kinds of marketing efforts; they do however provide empirical evidence for the marketing efforts for which data are available to academic researchers. These results confirm through independent epidemiological analysis that outreach and payments to physicians through the pharmaceutical companies was an important way in which the distribution of opioids across the United States was facilitated.

Finally, Powell et al. (2020)[142] examined the introduction of the Medicare Prescription Drug Benefit (Part D) program in 2006 as a potential driver of opioid use among those aged 65+. This paper is particularly informative given the quasi-experimental design of using an exposure with exogenous variation to assess the effects of changes in opioid use. "Exogenous variation" is a term that is commonly used in epidemiological and economics literature to mean that there is no possibility that confounding factors such as increased prevalence of pain, or increased risk factors for addiction, could explain changes in the exposure. Thus, changes in the Medicare insurance coverage cannot be caused by factors related to use, and for that reason, associations between changes in Medicare and changes in opioid use can be interpreted as causal. Using data from 1999 through 2016, the authors documented that the Medicare insurance expansion affected the opioid use, with states that had a relatively larger proportion of individuals gaining access to prescription drug coverage exhibiting an increase in opioid use based on ARCOS data. Further, the authors examined correlations with drug overdose deaths (specifically those with codes that indicate prescription opioid poisoning), as well as substance abuse treatment admissions (which is an indicator of the occurrence of opioid use disorders). For both prescription deaths and treatment admissions, there was evidence that the increase in the exogenous increase in opioid use caused by the insurance expansion was associated with increases in deaths and treatment admissions; results were robust to a range of sensitivity analyses, alternative modeling of the statistical associations, and a range of quasi-experimental statistical models. These data reinforce the conclusion that opioid use directly affects opioid-related harm, and provide a strong design and test of the hypothesis using the quasi-experimental instrument of changes in Medicare prescription coverage.

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